organized into different discrete niches each with unique characteristics including enrichment for specific cell populations. B cell were often organized into large clusters with CD4 T cells including T follicular helper-like cells. In contrast, the CD4- T cell populations formed small dispersed clusters which, on a per patient basis, predicted progression to ESRD ($p=0.004$).

Conclusions These data reveal that in LN, specific *in situ* inflammatory states are associated with the failure of conventional therapy and progression to ESRD.

Acknowledgments These studies were funded by the NIH Autoimmunity Centers of Excellence and Lupus Research Alliance.

505

PARENCHYMAL $\text{INF}\gamma$ RESPONSE REGULATES MURINE LUPUS NEPHRITIS

¹Minjung Kim, ²Anthony Marinov, ²Mark Shlomchik, ^{1,3}Jeremy Tilstra*. ¹Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, US; ²Department of Immunology, University of Pittsburgh School of Medicine, USA; ³Lupus Center of Excellence, UPMC, USA

10.1136/lupus-2021-lupus21century.23

Background Lupus nephritis is the most common life-threatening end-organ complication of SLE. Interstitial infiltrates, specifically T cells, are major predictors of disease outcomes. We recently determined that kidney-infiltrating T cells (KITs) are suppressed after kidney infiltration and exhibit an exhausted phenotype. Notably, the kidneys of nephritic lupus-prone (MRL.*Fas*^{lpr}) mice upregulate PD-L1, which we hypothesize is one mechanism inducing KIT suppression. $\text{INF}\gamma$ is the major inducer of PD-L1 and given the known role of $\text{INF}\gamma$ in lupus nephritis, we postulated that $\text{INF}\gamma$ induces a protective program in the kidneys of lupus-prone mice, in direct contrast to the proinflammatory role of $\text{INF}\gamma$ in the hematopoietic compartment.

Methods MRL. *Fas*^{lpr} mice develop autoantibodies, proteinuria, dermatitis, and glomerulonephritis. Others have previously shown that global $\text{INF}\gamma$ receptor deficiency ($\text{INF}\gamma\text{R}^{-/-}$) ameliorates disease in this mouse model. To determine if $\text{INF}\gamma$ signaling on parenchymal cells regulates disease, we generated bone marrow chimeras by transferring congenically labeled WT immune cells into either wild-type (WT) or $\text{INF}\gamma\text{R}^{-/-}$ MRL.*Fas*^{lpr} recipients. If our hypothesis is correct, then the $\text{INF}\gamma\text{R}^{-/-}$ recipients would have more severe disease than their WT counterparts. Chimerization occurred at 4-6 weeks of age and female and male mice were analyzed for disease pathology at 23 and 27 weeks post-chimerization respectively. Analysis included proteinuria, renal histology for both interstitial and glomerular disease, dermatitis, autoantibody production, and immune cell activation. Survival analysis was performed on female mice. Additional analysis focused specifically on T cell phenotypes.

Results $\text{INF}\gamma\text{R}^{-/-}$ MRL.*Fas*^{lpr} recipient mice exhibited more severe and rapid disease onset than WT recipient controls. While proteinuria was not different between the two groups, the $\text{INF}\gamma\text{R}^{-/-}$ recipients had more severe glomerulonephritis ($p < 0.005$) and interstitial disease ($p < 0.001$). Consistent with these findings, $\text{INF}\gamma\text{R}^{-/-}$ recipients had reduced survival ($p < 0.05$). As expected, $\text{INF}\gamma\text{R}$ deficiency resulted in reduced PD-L1 expression. When examining infiltrates, KITs isolated from $\text{INF}\gamma\text{R}^{-/-}$ recipients exhibited increased expression of Tim3 and PD-1.

Conclusions These experiments suggest that parenchymal $\text{INF}\gamma\text{R}$ signaling results in upregulation of protective mechanisms which reduce kidney disease and alter T cell phenotypes. This contrasts with global $\text{INF}\gamma\text{R}^{-/-}$ which ameliorated kidney disease. Overall, this finding argues that suppression of $\text{INF}\gamma$, and possible other inflammatory mediators, may have differential effects on specific cell lineages and that global suppression of $\text{INF}\gamma\text{R}$ may have both positive and negative effects on disease pathogenesis. This will need to be considered when devising targeted therapies.

Acknowledgments This work was supported by the Lupus Research Alliance (Novel Research Grant), NIAID (R01 AI137132), and J.T was supported by NIAMS 5K08AR075056.

506

BELIMUMAB (BEL) IMPROVES RENAL OUTCOMES IN ACTIVE LUPUS NEPHRITIS (LN): A PHASE 3 RANDOMIZED, PLACEBO (PBO)-CONTROLLED TRIAL

¹Brad H Rovin*, ²Frédéric Houssiau, ³Richard Furie, ⁴Ana Malvar, ⁵YK Onno Teng, ⁶Gabriel Contreras, ⁷Xueqing Yu, ⁸Beulah Ji, ⁹David Roth, ¹⁰Christi Kleoudis, ⁹Susan Makowiak, ⁹Anuradha Madan, ¹¹Jennifer Gilbride, ⁸Yulia Green. ¹The Ohio State University, Columbus, OH, USA; ²Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain and Service de Rhumatologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ³Northwell Health, Great Neck, NY, USA; ⁴Organizacion Medica de Investigacion, Buenos Aires, Argentina; ⁵Leiden University Medical Center, Leiden, the Netherlands; ⁶University of Miami Miller School of Medicine, Miami, FL, USA; ⁷Guangdong Provincial People's Hospital, Guangzhou, China; ⁸GlaxoSmithKline, Stockley Park, Uxbridge, UK; ⁹GlaxoSmithKline, Collegeville, PA, USA; ¹⁰Parexel, Durham, NC, USA; ¹¹GlaxoSmithKline, Stevenage, UK; †At the time of study

10.1136/lupus-2021-lupus21century.24

Background BEL is approved for patients (pts) with systemic lupus erythematosus (SLE). We evaluated intravenous (IV) BEL in active LN.

Methods This 104-week trial (GSK Study BEL114054; NCT01639339) randomized adults with active LN (class III, IV, and/or V) 1:1 to monthly BEL 10 mg/kg IV or PBO, plus standard therapy (ST) with high-dose corticosteroids + either cyclophosphamide (CyC) or mycophenolate mofetil (MMF) for induction at the investigator's discretion. CyC was followed by azathioprine (AZA), and MMF by MMF maintenance. The primary endpoint was Primary Efficacy Renal Response (PERR = urine protein:creatinine ratio [uPCR] ≤ 0.7 ; estimated glomerular filtration rate [eGFR] no more than 20% below pre-flare value or ≥ 60 ml/min/1.73m²; no rescue therapy) at Week 104. Other endpoints were Complete Renal Response (CRR = uPCR < 0.5 ; eGFR no more than 10% below pre-flare value or ≥ 90 ml/min/1.73 m²; no rescue therapy) at Week 104; time to renal event (end-stage kidney disease, doubling of serum creatinine, increased proteinuria and/or impaired renal function, renal disease-related treatment failure) or death. Endpoints were analyzed by ST regimen.

Results 224 pts were randomized to each arm. At Week 104, there were significantly more PERR and CRR responders on BEL vs PBO: (43.0% vs 32.3%, OR [95% CI] 1.6 [1.0, 2.3]; $p=0.03$) and (30.0% vs 19.7%, OR [95% CI] 1.7 [1.1, 2.7]; $p=0.02$), respectively. Risk of renal event or death was lower in BEL pts relative to PBO (HR [95% CI] 0.5 [0.3, 0.8]; $p < 0.01$). Week 104 PERR response rates in pts on CyC/AZA were 33.9% with BEL and 27.1% with PBO, and 46.3% with BEL vs 34.1% with PBO in those on MMF. BEL reduced risk of renal event or death on background of CYC/AZA (HR [95% CI] 0.5 [0.2, 1.0]) and MMF (HR [95% CI] 0.5 [0.3,